REMARKS

I. Amendments to the Claims

Claims 1-26 are all the claims currently pending in the application. Claims 1-6, 8-18, 20-23, 25 and 27 are withdrawn from consideration and claims 7, 19, 24 and 26 are currently rejected.

After entry of this amendment, claims 1-6, 8-23, and 25-33 will be all the claims pending in the application.

In the present amendment, claims 7 and 24 have been canceled.

Claim 19 has been redrafted in independent form to recite a method of inhibiting angiogenesis, comprising administering to a subject in need thereof an effective amount of a pharmaceutical composition comprising an isolated human ChM1L polypeptide having an effect of inhibiting angiogenesis, wherein said isolated human ChM1L polypeptide comprises a sequence as set forth in SEQ 1D NO: 2. Support for this amendment can be found throughout the specification and claims. In particular, page 16 of the specification discloses that ChM1L may be associated with angiogenesis-related diseases such as cancer.

Claim 26 has been redrafted in independent form to recite a method of inhibiting angiogenesis, comprising administering to a subject in need thereof an effective amount of an isolated human ChM1L polypeptide comprising the amino acid sequence as set forth in SEQ ID NO: 2 and having an effect of inhibiting angiogenesis. Support for this amendment can be found throughout the specification and claims.

New claims 28 and 29 recite methods of inhibiting angiogenesis, comprising administering to a subject in need thereof an effective amount of polypeptides that are at least 95% identical to SEQ ID NO: 2 and inhibit angiogenesis. Polypeptide variants generally are described at page 10, lines 21-28, and page 13, lines 9-13 of the specification. Variants with at least 95% identity are supported in the specification at page 27, and in Figure 1(b), wherein the full-length human ChM1L polypeptide is shown to be about 95% identical to ChM1L from mice and rats.

New claims 30 and 31 recite methods of inhibiting angiogenesis, comprising administering to a subject in need thereof an effective amount of soluble ChM1L polypeptides comprising amino acids 212 to 317 of SEQ ID NO: 2 and having the effect of inhibiting angiogenesis. Soluble ChM1L is described throughout the specification, especially at page 32 and in Examples 13 and 14.

New claims 32 and 33 recite methods of inhibiting angiogenesis, comprising administering to a subject in need thereof an effective amount of polypeptides that are at least 95% identical to amino acids 212 to 317 of SEQ ID NO: 2, wherein said polypeptides inhibit angiogenesis. As noted above, polypeptide variants are described in the specification at page 10, lines 21-28; page 13, lines 9-13; page 27; and in Figure 1(b).

II. Objection to the Claims

At page 2 of the Office Action, claims 19, 24 and 26 were objected to because each of these claims depends on non-elected claim 9.

Claims 19 and 26 have been redrafted in independent form so that they no longer depend on claim 9.

In addition, because claim 24 has been canceled, the objection is moot with regard to this claim.

Thus, Applicants respectfully request reconsideration and withdrawal of this objection.

III. Claim Rejections Under 35 U.S.C. § 112, 1st Paragraph –Written Description

At the bottom of page 2 of the Office Action, claims 7, 19, 24, and 26 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

Specifically, the Examiner contended that the claims encompass variants with unknown structure, because the term "substantially comprises" is defined in the specification such that the claimed polypeptides may have unlimited mutations, as long as they retain the function of SEQ ID NO: 2. The Examiner also stated that under U.S. patent practice, DNA and protein sequences cannot be claimed on the basis of function alone.

Claims 7 and 24 have been canceled, rendering the rejection moot as to these claims.

Claims 19 and 26 have been amended such that the claims no longer recite polypeptide variants, rendering the rejection moot as to these claims as well.

New claims 28, 29, 32, and 33 recite polypeptides that are "at least 95% identical to SEQ ID NO: 2" rather than polypeptides that "substantially comprise" SEQ ID NO: 2. The claimed polypeptides are also required to inhibit angiogenesis. Applicants submit that new claims 28, 29, 32, and 33 are sufficiently described, for at least the following reasons.

The procedures for making homologues of SEQ ID NO. 2 are disclosed at pages 10 and 13 in the specification and are conventional in the art. Furthermore, due to the structural

similarity of the members of the genera recited in the claims, one of ordinary skill in the art would expect that a substantial number of variants would possess the claimed activity. In addition, an assay is described at Example 14, pages 39 and 40 of the specification, which will identify other proteins having angiogenesis-inhibiting activity. Accordingly, a person of ordinary skill in the art would conclude that Applicants were in possession of the homologues encompassed by claims 28, 29, 32, and 33. See PTO Revised Interim Written Description Guidelines Training Materials, Example 14, pages 53-55.

Applicants respectfully request reconsideration and withdrawal of the written description rejection.

IV. Claim Rejections Under 35 U.S.C. § 112, 1st Paragraph – Enablement

A. At paragraph 1 at the bottom of page 6 of the Office Action, claims 7, 19, 24 and 26 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement.

Specifically, the Examiner contends that the specification, while being enabling for SEQ ID NO: 2, does not reasonably provide enablement for a polypeptide encoded by a human gene that "substantially" comprises the amino acid sequence as set forth in SEQ ID NO:2.

Claims 7 and 24 have been canceled, rendering the rejection moot as to these claims.

Claims 19 and 26 have been amended such that the claims no longer recite polypeptide variants, rendering the rejection moot as to these claims as well.

New claims 28, 29, 32, and 33 recite methods of using polypeptides that are "at least 95% identical to SEQ ID NO: 2" or "at least 95% identical to amino acids 212 to 317 of SEQ ID NO: 2" rather than polypeptides that "substantially comprise" SEQ ID NO: 2. The recited

polypeptides are also required to inhibit angiogenesis. Applicants submit that new claims 28, 29, 32, and 33 are sufficiently enabled, for at least the following reasons.

First, the procedures for making protein variants are discussed in the specification on pages 13, lines 6-19, are well known in the art, and entail routine rather than undue experimentation. Similarly, various techniques for isolating naturally-occurring DNA encoding functionally equivalent proteins are discussed in the specification on pages 13-14, and are also conventional in the art. In addition, the specification enables the identification of variants within the scope of the claims: ChM1L activity is defined on page 7, lines 4-5, as inhibition of angiogenesis, and an assay for detecting angiogenesis-inhibiting activity is described in Example 39 on page 28. Furthermore, the likelihood that claimed variants with at least 95% homology to the natural proteins will have angiogenesis-inhibiting activity is supported by the disclosure that the mouse and the rat homologues are about 95% homologous to the human ChM1L, yet presumably possess the recited activity.

Accordingly, Applicants respectfully request reconsideration and withdrawal of this aspect of the enablement rejection.

B. At paragraph 2 on page 10 of the Office Action, claims 19 and 26 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement.

The Examiner contended that the specification, while being enabling for SEQ ID NO: 2 inhibiting the formation of tube-like structures of human umbilical vein endothelial cells (HUVECs) *in vitro*, does not reasonably provide enablement for a "pharmaceutical composition" or for a polypeptide that inhibits angiogenesis *in vivo*. The Examiner explained that a "pharmaceutical composition" (claim 19) implies *in vivo* use. Because of the unpredictability in

the art of disease treatment, the Examiner concluded that the *in vitro* results using HUVECs do not enable the *in vivo* use of the claimed polypeptides.

Applicants respectfully traverse this rejection, and submit that a person of ordinary skill in the art would be able, without undue experimentation, to make and use the human ChM1L polypeptides for *in vivo* treatment and/or prevention of disease.

First, a number of angiogenesis inhibitors that target tumor vasculature have recently been identified using *in vitro* and *in vivo* anti-angiogenesis models. Several of these angiogenesis inhibitors, including endostatin and angiostatin, inhibit *in vitro* angiogenesis in human umbilical endothelial cells (HUVECS) (Kim et al., *Endostatin blocks vascular endothelial growth factor-mediated signaling via direct interaction with KDR/Flk-l,* 277 J Biol Chem. (2002), 27872-9; Dhanabal et al, *Cloning, expression, and in vitro activity of human endostatin*, 258 Biochem Biophys Res Commun. (1999), 345-52; and Claesson-Welsh et al., *Angiostatin induces endothelial cell apoptosis and activation of focal adhesion kinase independently of the integrin-binding motif RGD*, 95 Proc Natl Acad Sci (1998), 5579-83).

Systemic administration of these angiogenesis inhibitors in animals significantly suppresses the growth and metastases of a variety of tumors (0' Reilly et al., *Endostatin: an endogenous inhibitor of angiogenesis and tumor growth*, 88 Cell (1997), 277-85; Boehm et al., *Antiangiogenic therapy of experimental cancer does not induce acquired drug resistance* 390 Nature (1997), 404-7; and 0' Reilly et al., *Angiostatin: a novel angiogenesis inhibitor that mediates the suppression of metastases by a Lewis lung carcinoma,* 79 Cell (1994), 315-28). These reports suggest that angiogenesis inhibitors identified using *in vitro* angiogenesis models may inhibit *in vivo* angiogenesis, including tumor angiogenesis.

Recently, the United States Food and Drug Administration approved the first anti-angiogenesis drug, bevacizumab (Avastin, Genentech) as a treatment for patients with metastatic colorectal cancer. Avastin is a monoclonal antibody for vascular endothelial cell growth factor (VEGF). Anti-VEGF antibodies inhibit *in vitro* angiogenesis in HUVECs (Asano et al., *Inhibition of tumor growth and metastasis by an immunoneutralizing monoclonal antibody to human vascular endothelial growth factor/vascular permeability factor 121*, 55 Cancer Res. (1995), 5296-301); *in vivo* tumor growth in animals (*Id.* and Kim et al., *Inhibition of vascular endothelial growth factor- induced angiogenesis suppresses tumor growth in vivo*, 362 Nature (1993), 841-4) and in humans (Yang et al., *A randomized trial of bevacizumab, an antivascular endothelial growth factor antibody, for metastatic renal cancer*, 349 N Engl J Med. (2003), 427-34; Willett et al., *Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer*, 10 Natl. Med. (2004), 145-7; and Ferrara et al., *Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer*, 3 Natl Rev Drug Discov. (2004), 391-400).

The results outlined above demonstrate that angiogenesis inhibitors that have been characterized using *in vitro* angiogenesis assays using HUVECs are potential anti-angiogenesis drugs for human diseases such as tumors. Therefore, inhibition of HUVEC tube formation by ChMIL treatment indicates that ChMIL is a potential drug for inhibition of angiogenesis in treating tumors and other angiogenesis-related diseases.

In conclusion, the ability of a compound to inhibit angiogenesis in HUVECs would have been recognized by persons of ordinary skill in the art as reasonably correlating to the ability of

that same compound to act as an angiogenis inhibitor for *in vivo* treatment and/or prevention of specific disease conditions.

Accordingly, Applicants respectfully request reconsideration and withdrawal of this aspect of the enablement rejection.

V. Claim Rejections Under 35 U.S.C. § 102(e) - Anticipation

At page 14 of the Office Action, claims 7, 19, 24 and 26 were rejected under 35 U.S.C. § 102(e) as being anticipated by Baker et al., U.S. Publication No. 2003/0073129-A1 ('129) or Eaton et al., U.S. Publication No. 2002/0119130-A1 ('130).

Specifically, the Examiner stated that '129 and '130 each teach a sequence, SEQ ID NO: 322 and SEQ ID NO: 116, respectively, which is 100% identical to the claimed SEQ ID NO: 2, as shown by MPSRCH sequence similarity search.

Claims 7 and 24 have been canceled, rendering the rejection moot as to these claims.

Claim 19 has been amended to recite a method of inhibiting angiogenesis, comprising administering to a subject in need thereof an effective amount of a polypeptide comprising the amino acid sequence as set forth in SEQ 1D NO: 2 and having an effect of inhibiting angiogenesis. The polypeptides of claim 26 and new claims 28-33 also recite methods of inhibiting angiogenesis, comprising administering to a subject in need thereof an effective amount of polypeptides that inhibit angiogenesis.

Applicants submit that the cited references do not teach or suggest that the polypeptide of SEQ ID NO: 2 might inhibit angiogenesis, for at least the following reasons.

First, '129 and '130 do not disclose the results of any experiments demonstrating the activity of SEQ ID NO: 322 and SEQ ID NO: 116, respectively.

In addition, Applicants acknowledge that ChM-I, which shares some homology with SEQ ID NO: 2, has been shown to inhibit angiogenesis. However, because of the differences between ChM-1 and the polypeptides claimed in the present invention, a person of ordinary skill in the art would not reasonably have expected that the claimed polypeptides would inhibit angiogenesis.

Mature human ChM-I comprises a 120-amino acid residue C-terminal active domain, which contains eight cysteine residues and four disulfide bonds (Hiraki et al., *Identification of chondromodulin I as a novel endothelial cell growth inhibitor: purification and its localization in the avascular zone of epiphyseal cartilage*, 272 J Biol Chem. (1997), 32419-26). The C-terminal domain of ChM1L is only about 53% identical to the C-terminal 120 amino acid residues of ChMIL (see Fig. 1A of the present specification). In addition, although the C-terminal domains of both polypeptides contain eight cysteine residues, for one of the cysteine residues the position is not conserved (Fig. 1A). Furthermore, mature ChM-I is N-glycosylated, but soluble ChMIL has no glycosylation site (Hiraki et al.). Thus, although ChMIL has homology to ChM- I, the polypeptides differ significantly in amino acid sequence, cysteine position, and glycosylation.

As the Examiner pointed out in the outstanding Office Action, certain positions in the sequence of a protein are critical to the three dimensional structure/function relationship (Bowie et al., *Deciphering the message in protein sequences: tolerance to amino acid substitutions*, 247 Science (1990), 1306-10). The sensitivity of proteins to alterations of even a single amino acid, deletion of a single amino acid, and glycosylation are also exemplified in (Burgess et al.,

Possible dissociation of the heparinbinding and mitogenic activities of heparin-binding (acidic fibroblast) growth factor- l from its receptor-binding activities by site-directed mutagenesis of a single lysine residue, 111 J Cell Biol. (1990), 2129- 38; Gillies and Wesolowski, *Related antigen binding and biological activities of engineered mutant chimeric antibodies with human tumor specificities*, 1 Hum Antibodies Hybridomas (1990), 47-54; Lazar et al., *Transforming growth factor alpha: mutation of aspartic acid 47 and leucine 48 results in different biological activities*, 8 Mol Cell Biol. (1988), 1247-52; and Tao and Morrison, *Studies of aglycosylated chimeric mouse-human IgG: role of carbohydrate in the structure and effector functions mediated by the human IgG constant region,* 143 J Immunol. (1989), 2595- 601).

Thus, protein function must be characterized by actual experiments, and homology does not necessarily correlate to the same or similar function. The present inventors have characterized ChM1L for the first time, and have determined that the polypeptides of the present invention possess anti-angiogenic activity and are candidate anti-angiogenic drugs.

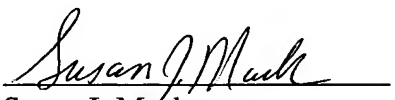
Therefore, Applicants submit that a person of ordinary skill in the art would not have reasonably expected that SEQ ID NO: 2 would possess anti-angiogenesis activity. Accordingly, Applicants respectfully request reconsideration and withdrawal of the anticipation rejection.

VI. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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